THE SYNTHESIS AND REACTIONS OF ISOINDOLE *N*-OXIDES

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Abstract. *Isoindole N-oxides are cyclic nitrones derived from isoindoles. The methods of their synthesis are presented comprehensively, including the recent developments based upon rhodium and palladium-catalyzed formation of the heterocyclic ring. Then, reactivity of isoindole N-oxides is presented, including the modern concept of the nitrone moiety of N-oxide acting as a directing group for Rh(III)- or Co(III)-catalyzed C–H activation, followed by intramolecular dipolar cycloaddition. Finally, the ability of isoindole N-oxides to act as radical traps to form nitroxyl radicals is briefly discussed.*

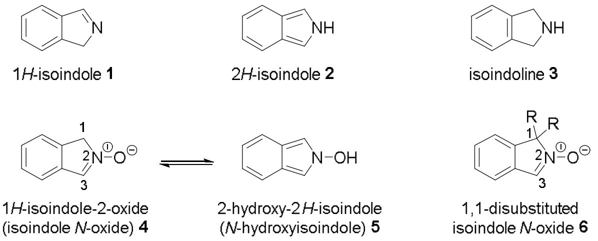
Contents

1. Introduction
2. Synthesis of isoindole *N*-oxides
  2.1. Condensation
  2.2. Oxidation
  2.3. Rhodium and palladium-catalyzed reactions
3. Reactions of isoindole *N*-oxides
  3.1. Nucleophilic addition
  3.2. Reduction
  3.3. Transition metal-catalyzed reactions with nitrone acting as a directing group
  3.4. Cycloaddition
  3.5. Free radical traps
4. Conclusions
References

1. Introduction

Isoindole[1] is a bicyclic ring system that contains condensed benzene and pyrrole-like rings. Unlike indoles, the nitrogen atom in isoindoles is not directly connected with the benzene ring (Scheme 1). In principle, two tautomeric forms of isoindole are possible, one with aromatic six-membered ring and a double bond in the five-membered ring (1*H*-isoindole), and the other with two double bonds in the smaller ring (2*H*-isoindole). Oxidation of the imine nitrogen in 1*H*-isoindole formally leads to 1*H*-ispoindole-2-oxide, or simply isoindole *N*-oxide.

Due to high resonance stabilization energy of benzene rings, the 1*H* form of *N*-oxide is usually thermodynamically more stable than the 2-hydroxyidole tautomer, even though the latter structure contains 10 π electrons in its cyclic system (Scheme 1).



Scheme 1. The structure of isoindoles, isoindole *N*-oxides and isoindolines.

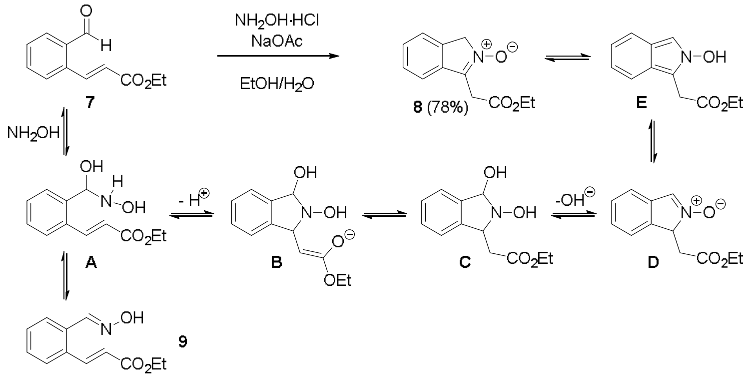
Among the examples reported in the literature, the sp^3-hybridized carbon atom of the five-membered ring is often disubstituted **6**, which locks the system in the former (1*H*) form. The five-membered, heterocyclic ring of 1*H*-ispoindole-2-oxide is not aromatic and, in consequence, isoindole *N*-oxides should be viewed as cyclic nitrones. Therefore, in general they undergo the reactions typical of nitrones, such as nucleophilic addition, or reduction to amines, imines or hydroxylamines. Owing to the rich chemistry of nitrones, isoindole *N*-oxides should be then ideal substrates for the preparation of biologically and pharmaceutically prevalent isoindolines **3** and isoindolinones.[2] In fact, isoindole *N*-oxides are only beginning to be exploited as synthetic intermediate because until recently they were a very poorly investigated group of heterocyclic compounds.

2. Synthesis of isoindole *N*-oxides

As a sub-class of nitrones, isoindole *N*-oxides are most often prepared using methods that are used for nitrones in general, that is oxidation of imines and condensation of carbonyl compounds with hydroxylamines. In recent years, versatile synthetic methods based upon rhodium or palladium catalysis have also been developed.

2.1. Condensation

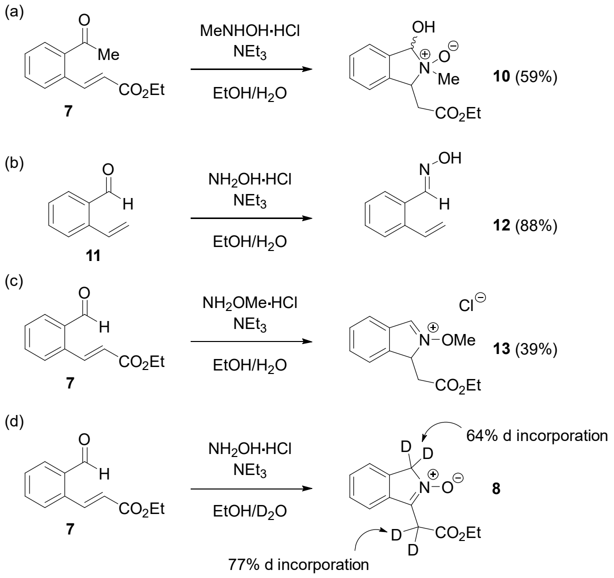
A simple, general and transition metal-free method of isoindole *N*-oxides synthesis was reported by the Bull group in 2015, who observed facile cyclization of a benzaldehyde **7** substituted at the *ortho* position with an α,β-unsaturated ester moiety (an ene-aldehyde), in the presence of aqueous hydroxylamine (Scheme 2).[3]



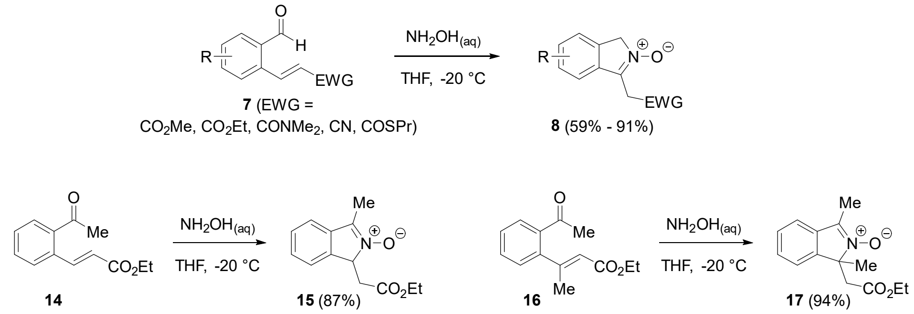
Scheme 2. Formation of isoindole *N*-oxides by condensation of ene-aldehydes with hydroxylamine.

A series of mechanistic experiments (Scheme 3) demonstrated that the formation of nitrone **8** occurred *via* nucleophilic attack of a *sp*^{3} nitrogen on the electron-poor double bond, followed by water elimination from intermediate **C** and tautomeric hydrogen shifts (*via* *N*-hydroxyisoindole **E**), leading to the product **8** with a more stabilized and more substituted double carbon-nitrogen bond. First, it was found that hydroxylamine hydrochloride alone produced oxime **9**, which further cyclized to nitrone **8** only in the presence of base. This result demonstrated the key role of base in facilitating the *aza*-Michael addition step. With *N*-methylhydroxylamine, the reaction stopped at the stage of 1-hydroxy-*N*-methylisoindoline *N*-oxide **10** (Scheme 3a). The reaction of 2-vinylbenzaldehyde **11** gave only the corresponding oxime **12**, confirming that the ring closure is a nucleophilic addition and not a reverse Cope cyclization, which would be faster with an electron rich double carbon-carbon bond (Scheme 3b). Reactions with *O*-methylhydroxylamine (Scheme 3c) and in the presence of D_2O (Scheme 3d) confirmed that the final stages involve tautomerisation *via* *N*-hydroxyisoindole, which is facilitated by external proton sources.

Under the optimized conditions (50% aqueous hydroxylamine, THF, −20 °C), a series of isoindole *N*-oxides **8**, **15**, and **17** were obtained, containing both electron-donating (OMe) and withdrawing (CF_3, pyridine nitrogen) groups in the aromatic ring (Scheme 4). Interestingly, in one case the *N*-hydroxyisoindole tautomer was found to be more stable. The same approach could be used to obtain dihydroisoquinoline *N*-oxides from substrates with the double bond separated from the ring by an additional methylene group.



Scheme 3. Elucidation of the mechanism of the condensation reaction.



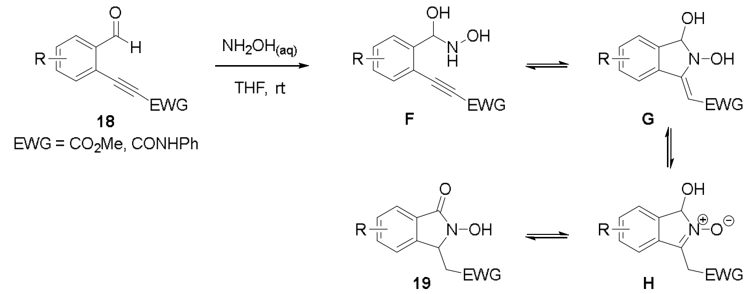
Scheme 4. Synthesis of isoindole *N*-oxides by condensation of ene-aldehydes with hydroxylamine.

Interestingly, a similar reaction of 2-akynyl-substituted benzaldehyde precursors **18** with hydroxylamine was reported to provide a general access to *N*-hydroxyisoindolones **19** (Scheme 5).[4] This outcome could be explained by the initial addition of hydroxylamine to form a hemiaminal which subsequently underwent intramolecular *aza*-Michael addition to the triple bond; the following double bond isomerization and enol-ketone tautomerism *via* intermediates **G** and **H** instead of water elimination led to the observed *N*-hydroxylactones **19**.

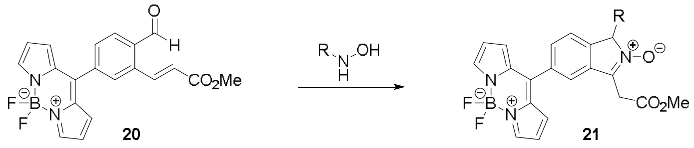
The methodology based upon cyclization of vinylbenzaldehydes was later applied in the design of a photochemical probe for hydroxylamine (Scheme 6).[5] In the presence of hydroxylamine (and its *N*-substituted derivatives) an arylaldehyde decorated with a suitably positioned electron deficient vinyl and a BODIPY core **20** underwent rapid cyclization to highly fluorescent BODIPY-conjugated isoindole *N*-oxide chromophore **21**. Unfortunately, the probe could not be used in cellular environment due to the presence of thiols (cysteine peptides *etc.*), which induced similar cyclization and fluorescent response.

Owing to its simplicity and general character, the condensation of ene-aldehydes with hydroxylamine became a method widely adapted by the synthetic community. An example of the hydroxylamine cyclocondensation route has been disclosed by Wang *et al.*, who designed a general route to (*Z*)-*ortho*-formyl- and ketocinnamates by an intramolecular Heck reaction.[6] The reaction of

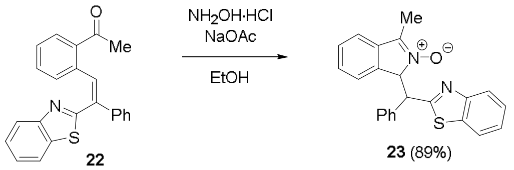
(*Z*)-3-(2-formylphenyl)crotonate with $NH_2OH{\cdot}HCl$ in the presence of Et_3N gave cyclic nitrone in high 88% yield. Similarly, condensation of $NH_2OH{\cdot}HCl$ with a triarylethylene **22** containing a benzothiazolyl and 2-acetylphenyl substituent at the double bond gave a 1-diarylmethylisoindole *N*-oxide derivative **23** (Scheme 7).[7]



Scheme 5. Formation of *N*-hydroxyisoindolones from alkynylarylaldehydes.



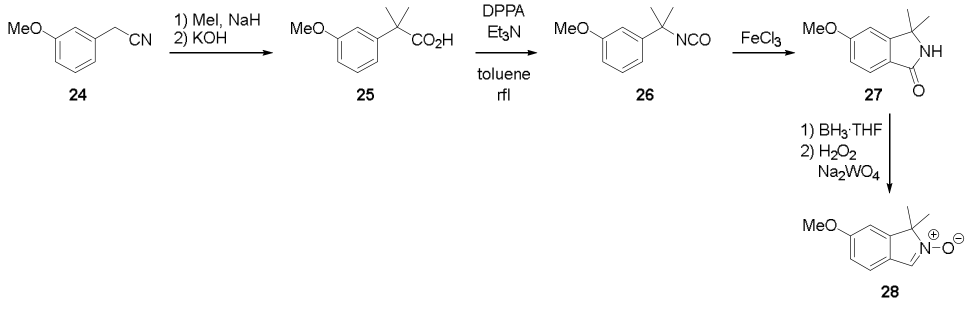
Scheme 6. A fluorescent probe for hydroxylamines.



Scheme 7. Condensation of hydroxylamine with triarylethylene.

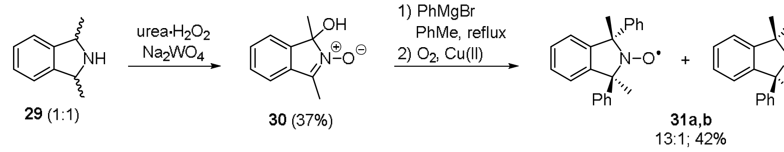
2.2. Oxidation

A general method of isoindole *N*-oxides synthesis is oxidation of isoindolines with H_2O_2/Na_2WO_4. For example, this approach was exploited by Fevig and co-workers.[8] In this case, the appropriate isoindoline was obtained by BH_3/THF reduction of the corresponding lactams **27**, which in turn were accessed by cyclization of aryl-substituted isocyanates **26** (Scheme 8).



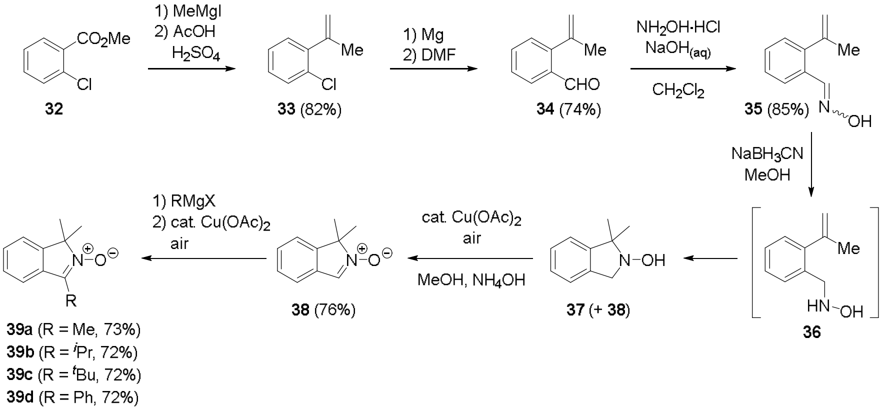
Scheme 8. Synthesis of isoindoline and its oxidation to isoindole *N*-oxide.

On the way to the synthesis of chiral nitroxides with C_2 symmetry, oxidation of a 1:1 diastereomeric mixture of 1,3-dimethylindolines **29** with urea-H_2O_2 complex was performed in the presence of Na_2WO_4 catalyst to provide 1,3-dimethyl-1-hydroxyisoindole-2-oxide **30** (Scheme 9).[9] This compound was further utilized in the synthesis of diastereomeric nitroxyl radicals **31a.b** by the reaction with an excess of PhMgBr and subsequent oxidation with O_2 catalyzed by Cu(II) salts.



Scheme 9. Oxidative preparation of isoindole *N*-oxide and of diastereoisomeric nitroxyl radicals.

A general route to 3-alkyl-1,1-dimethylisoindole *N*-oxides based upon formal oxidative nucleophilic substitution of hydrogen with Grignard reagents has been designed by Hatano and co-workers.[10] Methyl 2-chlorobenzoate **32** was transformed in two steps into 2-(2-chlorophenyl)propene **33** (Scheme 10). Chlorine-magnesium exchange and reaction with DMF provided aldehyde **34**, which was transformed into oxime and reduced with $NaBH_3CN$ into the corresponding *N*-arylmethylhydroxylamine **36**. Its spontaneous reverse Cope cyclization gave cyclic hydroxylamine **37** (in mixture with nitrone **38**), which was oxidized to isoindole *N*-oxide **38** with air in the presence of Cu(II) catalyst. Addition of Grignard reagents to the nitrone double bond of **38**, followed by another step of Cu(II)-catalyzed oxidation, gave the desired 3-alkyl derivatives **39a-d** of 1,1-dimethylisoindole *N*-oxides, including 1,1,3-trimethylisoindole *N*-oxide **39a** (TMINO).

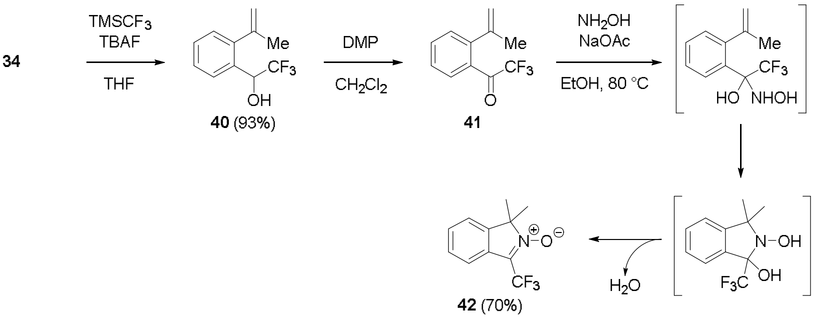


Scheme 10. An approach to isoindole *N*-oxides using reverse Cope cyclization.

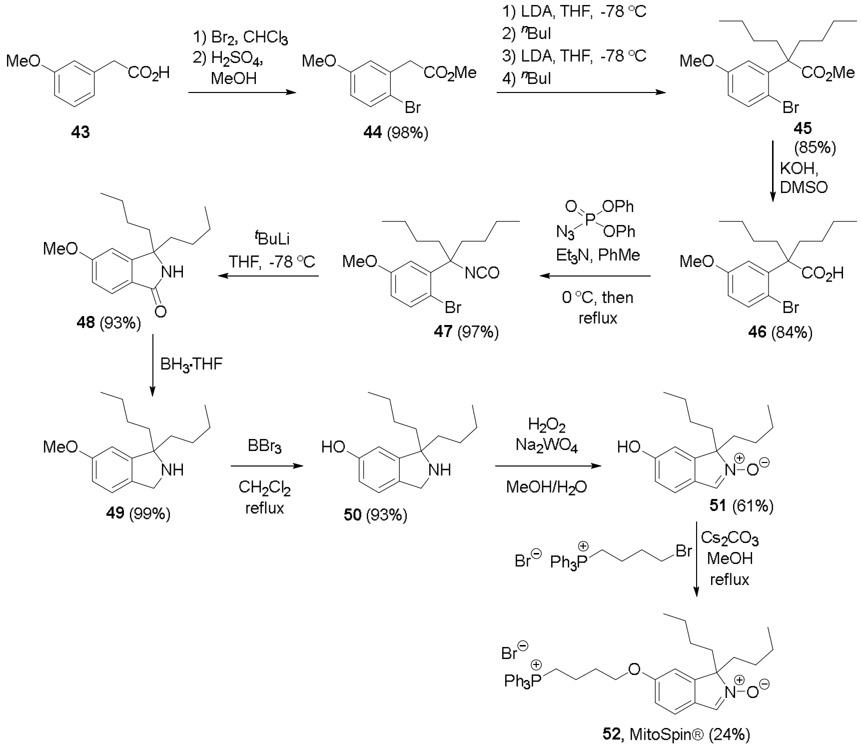
Reverse Cope cyclization of a hydroxylamine is probably the key step of another synthesis of the same group, this time of a trifluoromethyl isoindole *N*-oxide derivative (Scheme 11).[11] Addition of the Prakash reagent to aldehyde **34,** followed by Dess-Martin periodinane oxidation, gave unstable trifluoromethyl ketone **41**, which was further used without purification. Addition of hydroxylamine, reverse Cope cyclization and elimination of water provided the target compound **42**.

Hartley and co-workers designed MitoSpin® **52**, an isoindole *N*-oxide derivative intended as a trap for free radicals in mitochondria.[12] The multistep synthesis of this compound (Scheme 12) involved two sequential alkylations with LDA and ^{n}BuI to introduce the alkyl groups responsible for the desired ambiphilic properties at the α-position of ester **44**.. The heterocyclic ring was then formed by bromine-lithium exchange with ^{t}BuLi in **47** and cyclization of the resulting aryllithium onto the isocyanate group.

Further functional groups manipulations produced isoindoline **50**, which was oxidized with H_2O_2/Na_2WO_4 in moderate yield (61%).



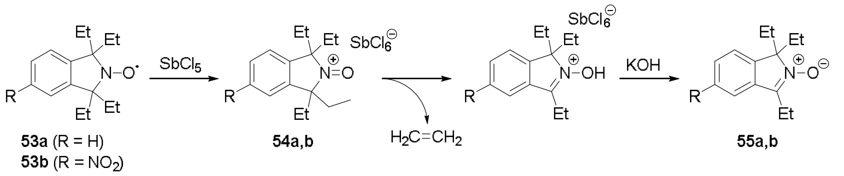
Scheme 11. Synthesis of a 3-trifluoromethylisoindole *N*-oxide.



Scheme 12. Synthesis of MitoSpin®.

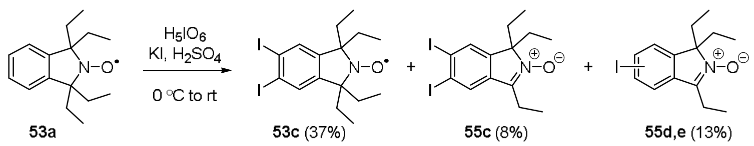
The Li group disclosed asymmetric [4+1]-spiroannulation of *O*-pivaloyl oximes with cyclic diazoamides (analogous to the reaction discussed in Section 2.3.) which led to spirocyclic isoindoles.[13] Oxidation of a selected product with *m*CPBA gave a spirocyclic isoindole *N*-oxide.

Another oxidative route to isoindole *N*-oxides is the oxidation of nitroxyl radicals, followed by fragmentation. It was already described by early investigators who reported oxidation of sterically hindered, cyclic nitroxyl radicals **53a,b** with $SbCl_5$ (Scheme 13).[14] These reactions led to oxoazonium salts **54a,b**, which were labile and underwent electrocyclic elimination of ethylene from the neighboring ethyl substituent with formation of protonated cyclic nitrones. The reaction was slower with a nitro group in the aryl ring then with unsubstituted nitroxyl radical. Free nitrones **55a,b** could be liberated upon the action of aqueous KOH.



Scheme 13. Synthesis of isoindole *N*-oxides by fragmentation of nitroxyl radicals.

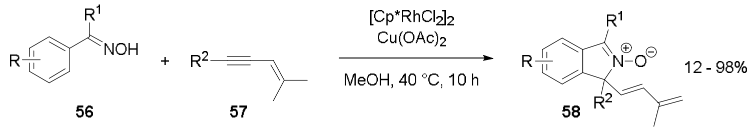
More recently, a similar process has been observed in an attempted synthesis of diiodo nitroxide **53c** bearing four ethyl groups vicinal to nitrogen.[15] In the presence of H_5IO_6 and KI in H_2SO_4, tetraethylnitroxide **53a** gave isomeric iodinated nitrones **55c-e** *via* elimination of ethylene, along with moderate yield of the expected product (Scheme 14).



Scheme 14. Formation of isoindole *N*-oxides during oxidation of a nitroxyl radical.

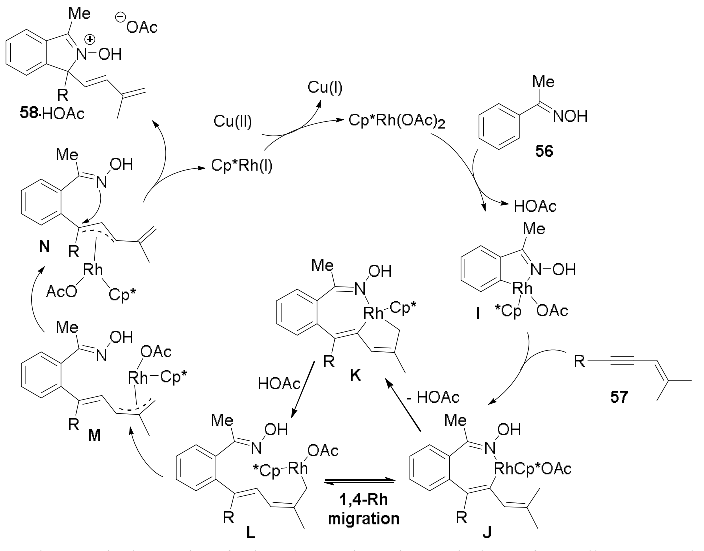
2.3. Rhodium and palladium-catalyzed reactions

A wide range of isoindole *N*-oxides functionalized with a dienyl substituent at C1 could be obtained in Rh(III)-catalyzed annulation of 1,3-dienynes **57** with oximes of aryl aldehydes and aryl ketones **56** (Scheme 15).[16] Apart from oximes, annulations of arylpyridines, phenanthridines, *N*-(2-pyridyl)isoquinolones and even 8-methylquinolines (for C*sp*^{3}–H activation) have been developed in this work. The design of these reactions involved 1,4-rhodium migration to enable 1,3-dienynes to act as C1 synthons and the source of the quaternary carbon center in the target products. 1-Dienyl-substituted isoindole *N*-oxides **58** with various alkyl, aryl, halogen or electron-withdrawing and donating groups in the aryl ring were obtained in high yields. Apart from 2-methyl-7-phenylhept-2-en-4-yne, enynes with –OH, –OTBS or –OTIPS groups could be employed, as well as enynes with various Ph, Me, and H substitution pattern at the double bond. Only the enyne with $-NMe_2$ substituent failed to react.



Scheme 15. Synthesis of spirocyclic isoindole *N*-oxides by Rh(III)-catalyzed annulation of 1,3-dienynes with oximes.

Efficient catalysis of the reaction with a rhodium complex obtained by cyclometalation of the starting oxime with $Cp^*Rh(OAc)_2$, as well as kinetic isotope effect determination led the authors to conclude that oxime-directed C–H activation of the aryl ring is the turnover-limiting step of the developed reaction. Further experiments with deuterated enynes supported the concept of 1,4-rhodium migration as the key step of the catalytic cycle (Scheme 16). Migratory insertion of the triple bond of **57** into the carbon-rhodium bond of intermediate **I** forms a vinyl rhodium complex **J**. 1,4-Rhodium migration (either direct od *via* allylic deprotonation and protonation) subsequently leads to a dienylated oxime which is coordinated to $Cp^*Rh(OAc)_2$ (intermediates **L**, **M**). Isomerization to a new allylic complex **N** (proximal to the aryl ring) and attack by the oxime nitrogen nucleophile forms the isoindole heterocyclic ring and Rh(I) species, which is reoxidized to Rh(III) by Cu(II) salts.



Scheme 16. The catalytic cycle of Rh(III)-catalyzed annulation of 1,3-dienynes with oximes.

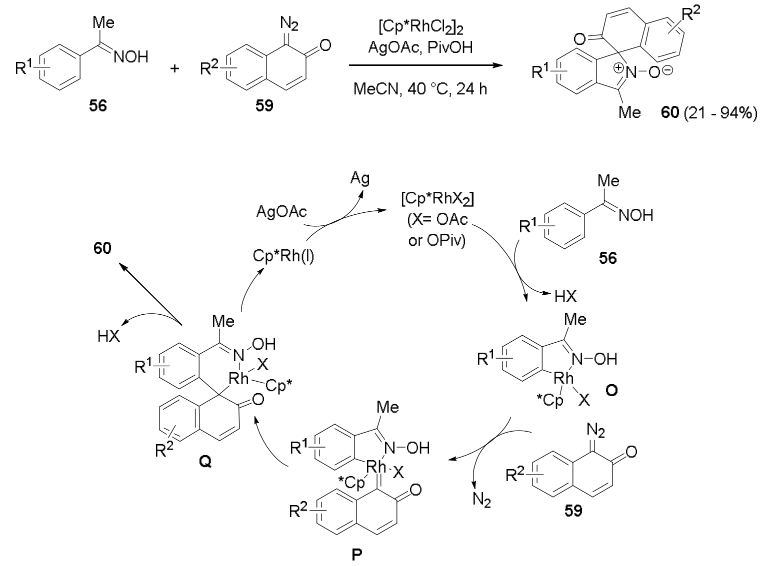
Another innovative strategy for the synthesis of spirocyclic isoindole *N*-oxides has been reported by the same group a year later.[17] The approach was based upon an oxidative [4+1]-spiroannulation reaction with 1-diazonaphthalen-1*H*-ones **59** as one carbon synthons, which reacted with oximes. In the presence of a rhodium(III) catalyst, pivalic acid and AgOAc as oxidant, a wide range of spirocyclic isoindole *N*-oxides **60** could be obtained in good or high yields from 1-diazonaphthalen-1*H*-one and oximes obtained from acetophenone derivatives bearing electron withdrawing or electron-donating substituents in the *para* or *ortho* positions of the phenyl ring (Scheme 17). *meta*-Substituted oximes reacted selectively at the less hindered side of the ring. Diazocompounds **59** with –OMe, –CO_2Me or –Br substituents in the aromatic ring could be used efficiently as well. Notably, using carboxylic acids instead of oximes led under similar conditions to spirocyclic isobenzofuranones. The catalytic isoindole *N*-oxides synthesis could be performed at a gram scale. One of the obtained products could be further subjected to selective reduction of the carbonyl group to give a single diastereoisomer of a spirocyclic alcohol.

The catalytic cycle was proposed to begin with oxime-directed, pivalate-assisted C–H activation of the aryl ring of **56** to form a rhodium metallacycle **O** (Scheme 17). Then, a rhodium carbene complex **P** is formed upon elimination of N_2 from 1-diazonaphthalen-1*H*-one. Migratory insertion of the aryl ligand and reductive elimination to form the C–N bond leads to the target spirocycle **60**.

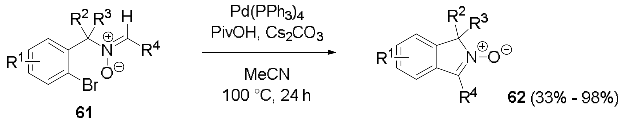
Palladium catalysis has been exploited recently for the development of quite a general approach to the isoindole *N*-oxide ring system.[18] Aldonitrones **61** bearing a 2-bromoarylmethyl group on the nitrogen were found to cyclize in the presence of $Pd(PPh_3)_4$ as a precatalyst to give cyclic nitrones **62** in a process of intramolecular C−H functionalization (Scheme 18). Pivalic acid was found to be crucial for obtaining good yields in this reaction.

A variety of isoindole *N*-oxides disubstituted at the C*sp*^{3} of the heterocyclic ring and bearing electron-withdrawing or donating groups in the aryl rings could be obtained (Scheme 18). It is worth noting that the product substituted with a nitro group in the six-membered ring of isoindole showed high propensity to add water to form a 1,2-dihydroxyisoindole derivative. *N*-Oxides bearing various aryl substituents (including heteroaryls like furyl or pyridyl) could also be obtained efficiently.

Moreover, highly sterically congested products **61** bearing an extended conjugated ring system and a 1-naphthyl substituent could be obtained under slightly harsher conditions (Scheme 19). The reaction was then found to work with some aldonitrones that were not derived from aryl aldehydes. For example, isoindole *N*-oxide with a *C*-cinnamyl substituent was obtained in high yield. The product of Myrtenal-derived aldonitrone coupling could also be obtained. Alkyl groups at C1 position were usually not accessible, with notable exception of the glyceraldehyde-derived substrate.



Scheme 17. Synthesis of spirocyclic isoindole *N*-oxides by Rh(III)-catalyzed spiroannulation of 1-diazonaphthalen-(1*H*)-ones with oximes.



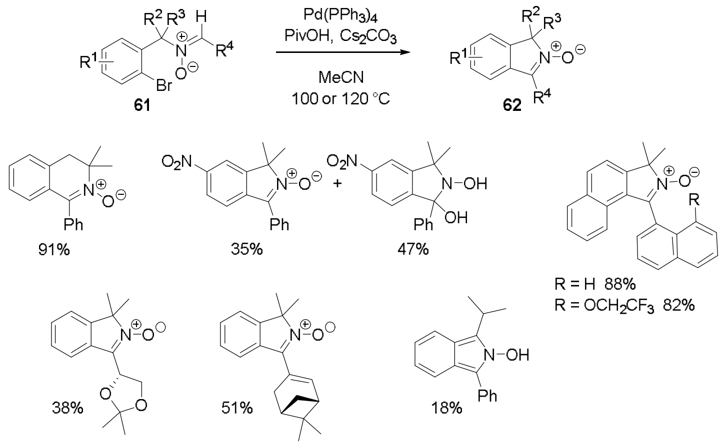
R^1 = H, F, Cl, -OCH$_2$O-
R^2, R^3 = Me, Me; Me, Bn; -(CH$_2$)$_4$-
R^4 = Ph, 2-furyl, 3-pyridyl, PhCH=CH-,
4-NCC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$,
2,4-OMeC$_6$H$_3$, 3-CF$_3$C$_6$H$_4$

Scheme 18. Synthesis of isoindole *N*-oxides by Pd-catalyzed cyclization of *N*-bromoarylmethyl aldonitrones.

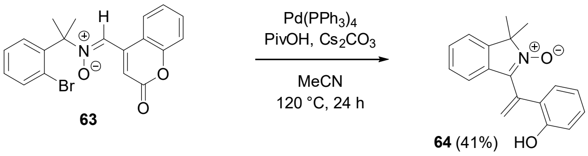
The importance of double substitution at the Csp^3 carbon of the forming pyrroline ring was demonstrated in the attempt to obtain 1-phenyl-3-isopropylisoindole *N*-oxide, which led only to low yield of tautomeric *N*-hydroxyisoindole. On the other hand, the reaction was found to be very efficient for the synthesis of dihydroisoquinoline derivatives.

The catalytic reaction of a coumarinyl substrate **63** was found to be accompanied by decarboxylation and eventually gave an isoindole *N*-oxide **64** functionalized with a 1-arylvinyl substituent at C3 (Scheme 20).

Mechanistic studies with nitrone substrates labeled with deuterium at the *C* position of nitrone resulted in very low KIE value, indicating that palladium catalyzed cyclization of *N*-bromoarylmethyl aldonitrones does not involve a direct C–H activation step. Instead, it probably proceeds *via* an attack of an arylpalladium species on the double C=N bond in analogy to the Heck reaction mechanism.



Scheme 19. Synthesis of isoindole *N*-oxides by Pd-catalyzed cyclization of *N*-bromoarylmethyl aldonitrones.



Scheme 20. Formation of 3-(1-arylvinyl)isoindole-*N*-oxide.

3. Reactions of isoindole *N*-oxides

3.1. Nucleophilic addition

Apart from the Grignard reagents additions discussed in the previous sections (see Schemes 9 and 10), 1,1-dimethyl-3-phenylisoindole *N*-oxide **65** has been reported to react with vinylmagnesium bromide to give a vinyl-functionalized hydroxylamine.[18]

3.2. Reduction

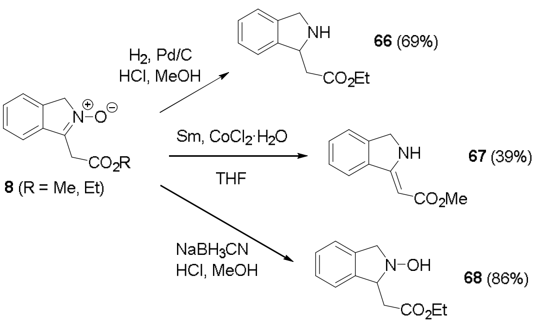
N-oxide **65** could be deoxygenated to the corresponding isoindole in the reaction with excess of $TiCl_4$ and $LiAlH_4$.[18]

Isoindole *N*-oxide **58** substituted with a dienyl chain at C1 could be selectively reduced to imine with Zn/NH_4Cl, whereas selective reduction of the two double carbon-carbon bonds was achieved with H_2 and a Pd catalyst.[16]

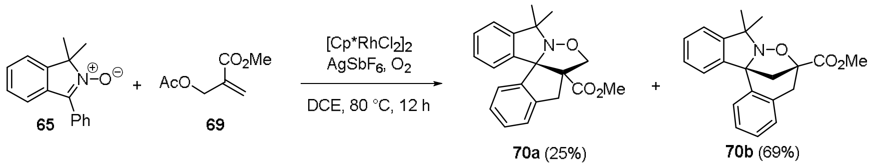
On the other hand, hydrogenation of 1-unsubstituted, 3-ethoxycarbonylmethylisoindole-2-oxide **8** in the presence of Pd/C in HCl/MeOH led to complete reduction of the nitrone moiety (Scheme 21).[3] Partial reduction of the same nitrone with $NaBH_3CN$ in HCl/MeOH gave a cyclic hydroxylamine *N*-hydroxyisoindoline **68**. Finally, reduction of the methoxycarbonyl analogue with samarium and $CoCl_2{\cdot}6H_2O$ led to deoxygenation and isomerization of the double bond to the more conjugated position to give enamine **67** in moderate yield.

3.3. Transition metal-catalyzed reactions with nitrone acting as a directing group

In the past few years, a few reports have appeared in which the nitrone functional group was used as a directing group for a transition metal (usually rhodium or sometimes ruthenium) catalyzed C–H activation in an aryl ring. This was followed by the introduction of an unsaturated moiety into that ring (usually a substituted allyl group) and then intramolecular dipolar cycloaddition between the introduced multiple bond and the nitrone moiety, thereby allowing for quick construction of nitrogen-containing polycyclic scaffolds. An example of such a rhodium-catalyzed process involving an isoindole *N*-oxide has been reported,[18] using the conditions developed by Kim and co-workers for activation of *N-tert*-butylaldonitrones (Scheme 22).[19] Isoindole *N*-oxide **65** reacted with a Morita-Baylis-Hillman adduct **69**, namely methyl 2-(acetoxymethyl)acrylate, in the presence of $AgSbF_6$, oxygen and $[Cp^*RhCl_2]_2$ to give regioisomeric, polycyclic isoxazolidines **70a,b** in high yield.

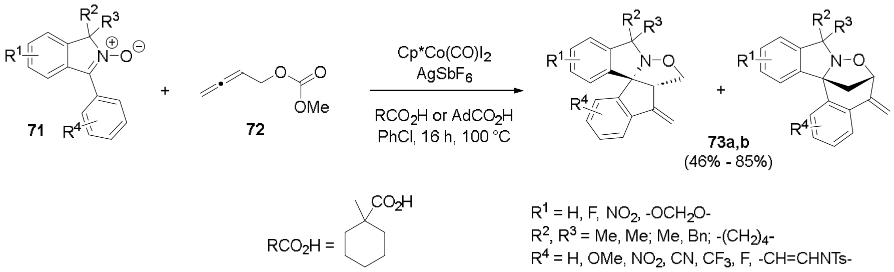


Scheme 21. Selective reduction of 1-unsubstituted, 3-alkyloxycarbonylmethylisoindole-2-oxide **8**.



Scheme 22. Rh(III)-catalyzed, nitrone directed C–H activation and annulation of isoindole *N*-oxide.

More recently, this efficient tandem strategy has been applied to isoindole *N*-oxides **71** bearing an aryl group at the five-membered ring, using a readily available cobalt catalyst instead of a rhodium complex.[20] In the presence of $Cp^*Co(CO)I_2$, a silver(I) salt, and 2,3-butadien-1-ols carbonates **72**, they underwent dienylation in the aryl ring *via* attack of an arylcobalt intermediate on the central carbon of the cumulene system (Scheme 23). The formed diene intermediates could not be isolated as they reacted further *via* a cycloaddition pathway to give complex, spirocyclic isoindolines **73a,b** bearing an exocyclic methylene function. Interestingly, a higher temperature was found to ensure much better regioselectivity of the cycloaddition step, providing good yields of the isomer **73a** with a condensed rather than bridged ring system. Spirocyclic isoindolines are found in the structure of several natural products and biologically active compounds.[21]

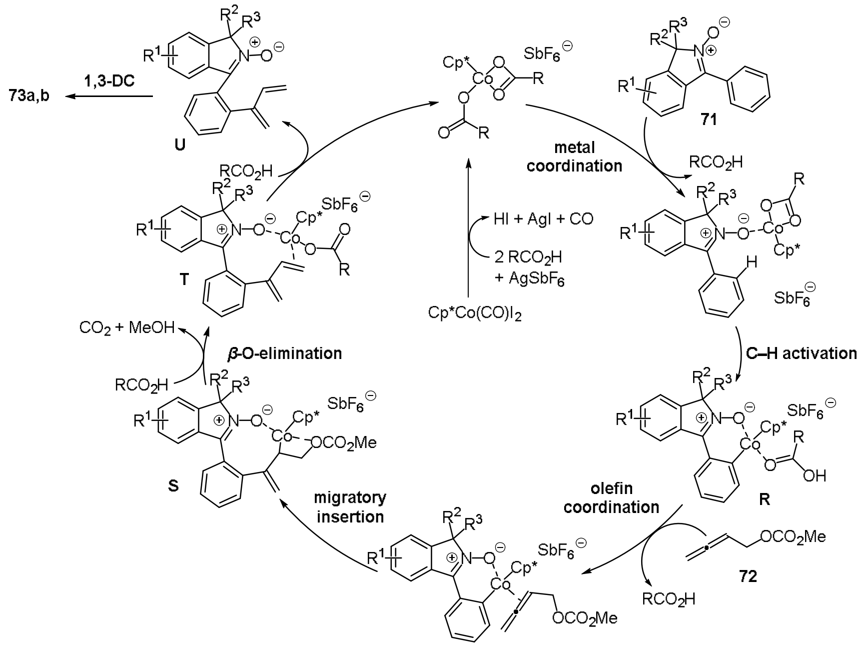


Scheme 23. Co(III)-catalyzed, nitrone directed C–H activation and annulation of isoindole *N*-oxides.

The reaction tolerated a wide range of substituents of very different electronic character (from methoxy to nitro) in both the isoindole and *C*-aryl benzene rings of **71**. The reaction scope includes also cyclic nitrones other than isoindoles, such as dihydroisoquinoline *N*-oxide or pyrroline *N*-oxides, giving access to spirocyclic pyrrolidines.

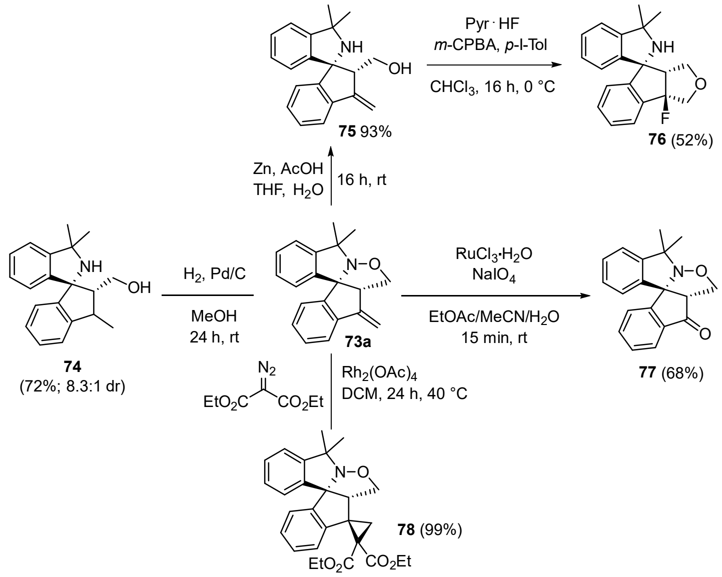
An interesting observation was made concerning the ability of the nitrone moiety to act as a directing group, depending on the molecular geometry. The substrate bearing a 2,4-dimethoxyphenyl ring as a substituent in which C−H activation was taking place was recovered unreacted (**71**, R^4=2,4-$(OMe)_2$). It was explained by the fact that the *ortho*-methoxy substituent prevents the substrate molecule from assuming a planar conformation, in which the cobalt atom associated with the nitrone oxygen atom could interact efficiently with the C−H bond of the aryl ring.

Control experiments in the presence of deuterated AcOH and with a substrate deuterated at the aryl ring supported the assumption that the reaction was initiated by a Co(III)-catalyzed C−H activation to form intermediate **R** (Scheme 24). The catalytic cycle presumably involves a carboxylate complex of cobalt, as the present of carboxylic acids, particularly 1-methylcyclohexanecarboxylic acid or adamantylcarboxylic acid, increased the reaction yield dramatically. Migratory insertion of the double bond of **72** proximal to the carbonate function produces intermediate **S**, which is then transformed into a dienylated isoindole *N*-oxide **U** (not detected) in the course of elimination of Co(III) carboxylate. Thermal, intramolecular dipolar cycloaddition of **U** leads to the observed regioisomeric products **73a** and **73b**.



Scheme 24. The catalytic cycle of the Co(III)-catalyzed, nitrone directed C–H activation and annulation.

The obtained indoline products **73** were found useful in further transformations leading to spirocyclic isoindolines (Scheme 25).[20] Catalytic hydrogenation cleaved the isoxazolidine N−O bond and reduced the methylene moiety to give spirocycle **74**. Selective reduction of the N−O bond with Zn/AcOH gave a spirocyclic homoallylic alcohol **75**, which could be further cyclized oxidatively to a fluorinated, polycyclic furane **76**. Oxidative cleavage of the double carbon-carbon bond introduced a carbonyl group **77**, whereas diastereoselective cyclopropanation of this bond could be readily achieved in the presence of diazomalonate and Rh_2-$(OAc)_4$ as catalyst **78**.

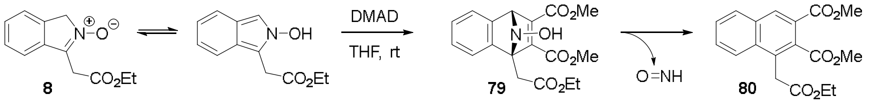


Scheme 25. Further transformations of spirocyclic isoindolines.

3.4. Cycloaddition

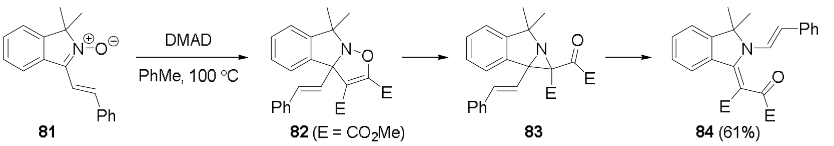
Isoindole *N*-oxides are relatively unreactive in intramolecular dipolar cycloaddition reactions. For example, in the reaction of *N*-phenylmaleimide with a diene-substituted isoindole *N*-oxide **58** selective [4+2]-cycloaddition occurred, with no 1,3-dipolar cycloaddition to the nitrone function.[16]

Isoindole *N*-oxides with at least one hydrogen atom at the C1 position preferentially react with dipolarophiles as their less stable *N*-hydroxyisoindole tautomers, in [4+2]- rather than [3+2]-cycloaddition mode. Bull and co-workers observed this behavior in cycloaddition with dimethyl acetylenedicarboxylate (DMAD), which led to a cycloadduct **79** with nitrogen occupying the bridgehead position (Scheme 26). It could be only detected by NMR and quickly underwent deaminative aromatization to naphthalene derivative **80**.



Scheme 26. [4+2]-Cycloaddition of DMAD with an isoindole-*N*-oxide.

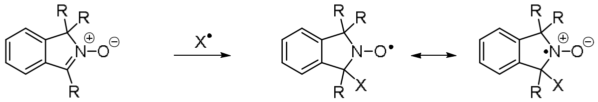
A different reaction course has been recently observed for 3-cinnamyl-1,1-dimethylisoindole *N*-oxide which upon reaction with DMAD rearranges to an *N*-cinnamylisoindoline **84** (Scheme 27).[18] This outcome can be explained by the rearrangement of the initial cycloadduct to aziridine **82**, by analogy to cycloaddition of DMAD to 3*H*-indole-1-oxides.[22] The following ring opening accompanied by the vinyl group migration to nitrogen accounts for the structure of the final product.



Scheme 27. Cycloaddition of DMAD 3-cinnamyl-1,1-dimethylisoindole *N*-oxide followed by rearrangement.

3.5. Free radical traps

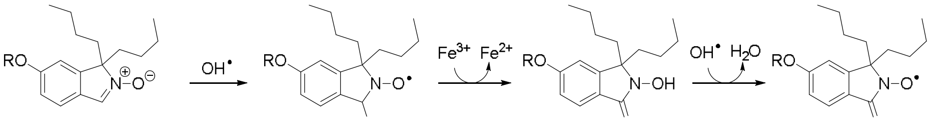
Free radicals add to the double carbon-nitrogen bond of isoindole *N*-oxides (and nitrones in general) to form nitroxyl radicals **85**, which can be relatively stable when sufficiently large substituents are present next to the nitrogen atom (Scheme 28). Higher stability of isoindole-derivatives as compared to other sterically hindered nitrones made isoindole *N*-oxides useful as spin traps for the EPR studies of oxygen-containing free radicals in biological systems.[8,10,15,23,24]



6 nitroxyl radical **85**

Scheme 28. Free radical addition to isoindole *N*-oxides.

In recent years, the Hartley group developed an ambiphilic isoindole *N*-oxide derivative MitoSpin® **52** for the studies of oxygen radicals in mitochondria (Scheme 29).



MitoSpin **52** (R = -$(CH_2)_4PPh_3^{\oplus}$ $Br^{\ominus}$) **86** **87** MitoSpinox **88**

Scheme 29. Free radical additions to MitoSpin®

4. Conclusions

For a long time, isoindole *N*-oxides remained a poorly explored group of heterocyclic compounds which were occasionally studied as a peculiar example of nitrones. Promising properties as spin traps led to increased interest in the synthesis of sterically hindered isoindole *N*-oxides. Only the recent years brought the development of general methods of preparing isoindole *N*-oxides decorated with various functional groups suitable for further transformations. Undoubtedly, these new developments will facilitate considerably the use of isoindole *N*-oxides as synthetic intermediates for accessing other five membered nitrogen-containing compounds, particularly the biologically relevant isoindolines.

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